REMARKS

Reconsideration of the present Application in view of the following remarks is respectfully requested. Claims 6-10 and 12-14 are currently pending.

REJECTION UNDER 35 U.S.C. § 101 AND 35 U.S.C. § 112, FIRST PARAGRAPH

The PTO rejects claims 6-10 and 12-14 under 35 U.S.C. § 101, alleging that the claimed polynucleotide lacks a specific, substantial, and credible utility and a well-established utility. The PTO asserts that without a demonstration otherwise, the claimed polynucleotide could have another catalytic activity, such as a phospholipase activity, which the PTO alleges is taught in Acton (U.S. Patent No. 6,268,135). The PTO further asserts that the phosphatase activities of the polypeptides disclosed in U.S. Patent Nos. 6,258,528 and 6,132,964 do not support Applicants' assertion that the presently claimed polynucleotide encodes a dual specificity phosphatase.

The PTO also rejects claims 6-10 and 12-14 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. In particular, the PTO asserts that the claimed invention has neither a specific, substantial, and credible utility nor a well-established utility, and therefore, allegedly, a person skilled in the art would not know how to make and use the claimed invention.

Applicants respectfully traverse these rejections and submit that the PTO has failed to set forth a *prima facie* case showing that the subject matter of the instant claims lacks utility. The presently claimed subject matter relates to isolated polynucleotides that encode a polypeptide having a conserved dual specificity phosphatase active site and that also have high homology to known, enzymatically active members of the dual specificity phosphatase family. Moreover, actual phosphatase activity of a DSP-14 polypeptide encoded by a claimed polynucleotide has been demonstrated, as described in the Declaration submitted herewith. As also described in the accompanying Declaration, mutation of the claimed DSP-14 encoding polynucleotides at sites homologous to those known to compromise the enzymatic activity in structurally related, *bona fide* members of the dual specificity phosphatase family of proteins resulted in DSP-14 polypeptides having decreased enzymatic activity. Applicants therefore

submit that, for reasons discussed in greater detail below, there can be no doubt that the present invention satisfies the utility requirements of 35 U.S.C. § 101.

Applicants' invention is directed in pertinent part to an isolated polynucleotide that encodes a polypeptide comprising the sequence of DSP-14 set forth in SEQ ID NO:2, wherein the polypeptide has the ability to dephosphorylate an activated MAP-kinase; and to related compositions and methods. For reasons also previously made of record, the presently claimed DSP-14 encoding polynucleotides, and their use in the claimed method for producing a DSP-14 polypeptide, have a well-established utility and a specific, substantial, and credible utility. Applicants further submit that a person having ordinary skill in the art will immediately appreciate the usefulness of the invention based on its characteristics, which are described in the specification and recited in the instant claims.

Briefly, the presently claimed polynucleotides (*e.g.,* SEQ ID NO:1) encode polypeptides that have extensive sequence homology to known dual specificity phosphatases (*e.g.,* application, Figure 3) and that contain a protein tyrosine phosphatase active site motif (*see, e.g.,* specification, page 13, lines 1-2) that is conserved in dual specificity phosphatases (*see, e.g.*, page 46, lines 8-14, and references cited therein). As understood in the art and disclosed in the present application, dual specificity phosphatases belong to the larger family of protein tyrosine phosphatases that share a conserved catalytic domain containing a cysteine residue situated N-terminal to a stretch of five variable amino acids followed by an arginine residue (*see, e.g.,* specification at page 46, lines 8-14 and cited reference: Fauman et al., *Trends in Biochem. Sci.* 21:413-17 (1996); *see also* Jia, *Biochem. Cell Biol.* 75:17-26 (1997); Flint et al., *Proc. Natl. Acad. Sci. USA* 94:1680-85 (1997)).

In addition, the present specification explicitly teaches that the conserved protein tyrosine phosphatase active site motif (-C-X_5-R-) is contained within the encoded DSP-14 polypeptide active site domain and comprises the amino acid sequence, VHCVMGRSRSATLVLAYLM (SEQ ID NO:3). (*See, e.g.,* page 8, lines 24-25; page 13, lines 1-2; SEQ ID NO:2 at amino acid positions 145-163; Fig. 3). Furthermore, the full-length DSP-14 polypeptide (SEQ ID NO:2) encoded by the subject invention polynucleotides shows significant homology to other MAP-kinase phosphatases, which are members of the dual

specificity phosphatase family (*see, e.g.*, specification, page 13, lines 7-8; Figure 3). On the basis of the identified active site motif and the homology of the encoded DSP-14 polypeptide with other dual specificity phosphatase family members, a person having ordinary skill in the art would reasonably believe that the DSP-14 polypeptide described in the instant specification has the specific ability to dephosphorylate an activated MAP-kinase.

Applicants respectfully submit that the PTO, by alleging that the instant application merely discloses "some 'conserved fragment'" (Action, at page 3, line 4), apparently fails to appreciate (i) that dual specificity phosphatases comprise a subset of protein tyrosine phosphatases (PTPs), as discussed herein and as disclosed in the present application and known to the art; and (ii) that the DSP-14 polypeptide sequence encoded by the presently claimed polynucleotides displays extensive and significant homology to many other members of the dual specificity phosphatase subfamily of PTPs. On this point, the Examiner's attention is respectfully directed to the application and drawings, for example, to the amino acid sequence alignment of DSP-14 with other dual specificity phosphatases in Figure 3. Accordingly, Applicants submit that reference by the PTO to DSP-14 as merely comprising "some 'conserved fragment'" is a mischaracterization, where significant sequence homology to other dual specificity phosphatases is apparent over much of the catalytic domain.

In further support of the utility of the claimed subject matter, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 by Ralf M. Luche, Ph.D., a co-inventor of the presently claimed invention, presenting evidence showing that the claimed polynucleotides encode polypeptides having dual specificity phosphatase catalytic activity. The Declaration presents data from experiments that were performed using methods known in the art and disclosed in the instant application for insertion of the claimed polynucleotide into an expression vector, transfection of the vector into a host cell, expression of the encoded DSP-14 polypeptide, and dephosphorylation of a phosphorylated substrate by the DSP-14 enzyme. As described in the instant Application and supported by the Declaration submitted herewith, the claimed DSP-14 polynucleotides have several specific and substantial uses that include, for instance, producing the encoded DSP-14 polypeptide; generating DSP-14 substrate trapping mutants, which may be used for characterizing and identifying DSP-14 substrates; and identifying agents

that alter intracellular molecular signaling by modulating DSP-14 activity (*see, e.g.*, specification, at page 7, line 12 through page 8, line 5; page 37, line 7 through page 40, line 12).

As also previously made of record and for reasons discussed herein, Applicants respectfully disagree with the assertion by the PTO that the claimed polynucleotides lack utility in view of the prior art. With particular regard to Acton (U.S. Patent No. 6,268,135) ('135), Applicants traverse the allegation made by the PTO that based on the disclosure in '135, the DSP-14 polypeptide encoded by the presently claimed polynucleotide could have other activities such as phospholipase activity.

As a preliminary matter, the PTO errs in its assertion that the presumption of validity of '135 under 35 U.S.C. § 282 necessarily extends to a presumption that all subject matter encompassed by the claims of '135 possesses "phospholipase utility" (Action, page 3, line 12), apparently a reference to "phospholipase activity" (*cf.* Action, page 3, line 8; *see also* Office Action of March 6, 2002, Paper No. 8, at page 5, line 2, which refers to "*enzymatic* activities such as phospholipase taught by Acton" (emphasis added)). Phospholipase *enzymatic* activity (*e.g.*, "binding a calcium ion to thereby release fatty acids from the second carbon group of glycerol of a phospholipid" ('135 at column 7, lines 56-58)) is not a recited feature of any issued claim in '135, nor for that matter is any phospholipase *activity* a recited element in any '135 claim. Accordingly, while the issued claims of '135 are certainly entitled to a proper presumption of validity under 35 U.S.C. § 282 (*i.e.*, the encompassed subject matter is presumed to satisfy the utility requirement), the PTO fails to establish any basis from which it can be concluded that the utility of SEQ ID NO:2 as disclosed in '135 *necessarily* derives from phospholipase enzymatic activity. "The claimed invention is the focus of the utility requirement." M.P.E.P. 2107.02[I]. To avoid raising issues that are not relevant to examination of a claim, unclaimed results, limitations or embodiments of an invention should not be read into a claim. *Id.*, citing *Carl Zeiss Stiftung v. Renishaw PLC*, 945 F.2d 1173, 20 USPQ2d 1094 (Fed.Cir. 1991); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961).

Applicants therefore respectfully submit that the citation by the PTO to 35 U.S.C. § 282 is inappropriate because the instant question is not one of whether or not '135 is a valid

patent. Instead the issue is whether the presently claimed subject matter, which relates to a DSP-14 encoding polynucleotide, satisfies the utility requirement under 35 U.S.C. § 101. For reasons provided herein and in the accompanying Declaration, the instant claims clearly comport with the requirements of 35 U.S.C. § 101.

Applicants submit that a person having ordinary skill in the art would consider credible that the polypeptide sequence disclosed in the '135 patent as SEQ ID NO:2 is that of an enzyme with dual specificity phosphatase activity, and would be extremely unlikely to believe that such a polypeptide sequence could be that of an enzyme with phospholipase activity, despite the name arbitrarily assigned to it (cardiovascular system associated phospholipase, or "CSAPL") (*see also* Declaration submitted herewith). This conclusion is supported by the disclosure in the '135 patent, which teaches that the CSAPL polypeptide (SEQ ID NO:2, '135) exhibits significant amino acid sequence similarity to a known dual specificity phosphatase, dual specificity protein phosphatase 3 (Accession No. P51452, "approximately 37% identical (over CSAPL amino acids 1-199)" ('135, at column 56, lines 19-29) [*sic*; CSAPL set forth in SEQ ID NO:2 has 198 amino acids]. In concurrence with these teachings, CSAPL (SEQ ID NO:2) contains the protein tyrosine phosphatase (PTP) catalytic site motif -C-X_5-R-, which can be found at positions 138-144 of SEQ ID NO:2 disclosed in the '135 patent. The conserved PTP catalytic site motif is well known in the PTP art (*see, e.g.*, instant specification, at page 46, lines 8-14; *see also* Keyes, *Biochim. Biophys. Acta* 1265:152-60; Fauman et al., *Trends in Biochem. Sci.* 21:413-17 (1996); Jia, *Biochem. Cell Biol.* 75:17-26 (1997); Flint et al., *Proc. Natl. Acad. Sci. USA* 94:1680-85 (1997); U.S. Patent No. 6,258,582, at column 13, lines 4-18; U.S. Patent No. 6,132,964 at column 13, lines 21-40 and SEQ ID NO:4 therein).

By contrast, although '135 elsewhere asserts that CSAPL preferably possesses a phospholipase A_2 active site (*i.e.*, the consensus sequence CCX_2HX_2C; *see* '135, at column 7, lines 60-65) located at amino acid positions 131-138 of SEQ ID NO:2 therein (column 8, lines 3-6), inspection of SEQ ID NO:2 reveals that amino acids 131-138, which are QGRVLVHC, fail to conform to the phospholipase A_2 active site consensus sequence (CCX_2HX_2C). Additionally, *no* portion of SEQ ID NO:2 as disclosed in '135 contains the phospholipase A_2 active site motif.

Applicants therefore respectfully submit that a skilled artisan could not reasonably conclude that SEQ ID NO:2 as disclosed in '135 is a polypeptide that has phospholipase A_2 structure or activity, but would instead be more likely to believe that the CSAPL polypeptide is a member of the dual specificity phosphatase family.

Therefore, and contrary to the assertions found in the Action, '135 provides no reasonable basis for a skilled artisan to doubt that the polynucleotides recited in the instant claims encode a dual specificity phosphatase, DSP-14. Applicants hasten to point out that, as discussed above, this conclusion is not a challenge to the validity of the '135 patent, but is presented instead in traversal of the PTO's assertion regarding what the skilled artisan would find credible given the instant claims in view of '135. Applicants therefore reiterate that the PTO fails to show that the patentable subject matter validly encompassed by the claims of '135 necessarily relates to utility that derives from phospholipase enzymatic activity, and that the PTO also fails to establish on what basis a person skilled in the art would consider SEQ ID NO:2 of '135 to have phospholipase enzymatic activity but not dual specificity phosphatase activity.

Applicants additionally submit that, contrary to the assertion made by the PTO (Action, page 3, lines 13-17), the instant specification discloses that

> [d]ual specificity phosphatases belong to the larger family of protein tyrosine phosphatases (PTPs) that share a conserved catalytic domain containing a cysteine residue situated N-terminal to a stretch of five variable amino acids followed by an arginine residue (Fauman et al., *Trends In Bioch. Sci.* 21:413-417, 1996). DSPs typically contain a PTP active site motif but lack sequence homology to PTPs in other regions (Jia, *Biochem. and Cell Biol.* 75:17-26, 1997). (Page 46, lines 9-14).

The specification further teaches that "[d]ual-specificity protein tyrosine phosphatases (dual-specificity phosphatases) are phosphatases that dephosphorylate both phosphotyrosine and phosphothreonine/serine residues (Walton et al., *Ann. Rev. Biochem.* 62:101-120, 1993)." (Page 2, lines 5-7). As discussed above, the conserved protein tyrosine phosphatase active site motif (-C-X_5-R-) is contained within the DSP-14 polypeptide encoded by the presently claimed polynucleotides and comprises the sequence, VHCVMGRSRSATLVLAYLM (SEQ ID NO:3). (*See, e.g.,* specification page 8, lines 24-25; page 13, lines 1-2; SEQ ID NO:2 at amino acid

positions 145-163). Applicants therefore submit that the PTO errs in its assertion that dual specificity phosphatases identified in the instant application are " a distinct family of enzymes" from the family that includes Ser/Thr and Tyr phosphatases; the PTO also errs by asserting that "homologous domains in other enzymes" are not a diagnostic feature for a specific family of enzymes.

Insofar as the PTO makes these errant assertions in support of its allegation that a person skilled in the art would not find it credible that the claimed polynucleotide usefully encodes a phosphatase, Applicants traverse. On the contrary, and in view of the accompanying Declaration as well as for reasons previously made of record, for example, in view of the non-DSP-14 sequences shown in Fig. 3 of the instant application, and the dual specificity phosphatase sequences disclosed in U.S. Patent Nos. 6,132,964 ('964) and 6,258,582 ('582), the claimed DSP-14-encoding polynucleotide and its DSP-14 polypeptide products have a specific and substantial utility that a person skilled in the art would find credible, based on regions of conserved sequence homologies that are shared by DSP-14 and other DSP's.

The '964 patent discloses that HHLM-4 (SEQ ID NO:4 therein) "has a *tyrosine protein phosphatase active site signature sequence* V146 through L158" (VHCAVGVSRSATL) (*see* column 13, lines 24-25; SEQ ID NO:4, emphasis added) and "has chemical and structural homology with a human *dual-specificity protein phosphatase*" (column 13, lines 29-31, emphasis added). Similarly, '582 discloses that

> the term "protein tyrosine phosphatase" or "PTPase" includes a protein or polypeptide (e.g., an enzyme) which is capable of facilitating (e.g., catalyzing) the removal of a phosphate group attached to a tyrosine, serine or threonine residue of a protein or polypeptides (e.g., a phosphoprotein). As referred to herein, a protein tyrosine phosphatase includes at least one catalytic domain having a specificity for (i.e. a *specificity to dephosphorylating tyrosine residues or both serine/threonine residues and tyrosine residues* (e.g., *the dual specificity PTPases*).... (column 9, lines 52-61(emphasis added)).

'582 further teaches that the disclosed CSAPTP polypeptides contain an extended catalytic active domain (VXVHCXAGXSRSXTX(3)AYLM), which is capable of facilitating the removal of a phosphate group attached to a tyrosine, serine, or threonine residue of a phosphoprotein (column 12, lines 35-38; see also, column 25, lines 18-25). Therefore, '964 and '582 and the present

application all disclose polynucleotides that encode members of the dual specificity phosphatase family, which members share certain structural homology regions.

Applicants further submit that the claimed polynucleotides encoding a DSP-14 polypeptide have a substantial and real world use. For reasons already of record, Applicants submit that the isolated polynucleotide of the present invention has a substantial utility with a real-world application, in that the subject invention polynucleotides encode a novel, dual specificity phosphatase and that dual specificity phosphatases regulate MAP-kinase signal transduction cascades. As disclosed in the specification, persons having ordinary skill in the art would readily appreciate that MAP-kinases are components of conserved cellular signal transduction pathways (*see*, *e.g.*, page 1, line 22 through page 2, line 4).

The physiological role of MAP-kinase signaling has been correlated with cellular events, such as proliferation, oncogenesis, development, and differentiation (*see*, *e.g.*, page 1, line 29 through page 2, line 4); therefore, expression and activity of dual specificity phosphatases are significant to the regulation of these MAP-kinase-mediated cellular functions. Persons skilled in the art appreciate that MAP-kinases are inactivated through dephosphorylation by dual specificity phosphatases, which is likely an important regulatory mechanism (*see, e.g.,* specification, page 1, lines 20-25; Muda et al., *J. Biol. Chem.* 272:5141 (1997), introduction; provided herewith for the Examiner's convenience; Keyes, *Biochim. Biophys. Acta* 1265:152-60 (1995), page 153; provided herewith for the Examiner's convenience). Whether multiple dual specificity phosphatases are required to regulate the multiple genes and splice variants of MAP kinases (*e.g.,* ERK, JNK/SAPK, and p38 kinase) is a "critical unanswered question." (*See* Muda et al., *supra*, page 5142-43). Applicants therefore submit that persons skilled in the art would immediately appreciate that the claimed polynucleotides encoding a novel dual specificity phosphatase would be useful for characterizing MAP kinase pathways. Therefore, and by way of example, a specific and substantial use of the present invention disclosed in the instant specification includes identification of agents capable of modulating cellular proliferative responses (*see* specification, page 2, lines 27-28), which contributes to understanding the

regulation of dual specificity phosphatases within MAP-kinase cascades, and which may lead to development of therapeutics for treating diseases relating to abnormal cell proliferation.

Moreover, and with regard to enablement, Applicants respectfully traverse the rejection under 35 U.S.C. § 112, first paragraph, and submit that the instant specification provides sufficient disclosure to teach a person having ordinary skill in the art how to make and use the claimed invention. For reasons already made of record, Applicants submit that the present Application teaches a skilled person how to make and use, readily and without undue experimentation, an isolated polynucleotide that encodes a DSP-14 polypeptide comprising the amino acid sequence set forth in SEQ ID NO:2, wherein the polypeptide has the ability to dephosphorylate an activated MAP-kinase, and how to make and use related compositions and methods, including a method of producing a DSP-14 polypeptide. Applicants further submit that the Declaration submitted herewith presents evidence that the present Application satisfies the requirements of 35 U.S.C. § 112, first paragraph, and also as discussed in detail above, that the claimed polynucleotides encode an enzyme that relates to a phosphatase and not to a phospholipase.

The specification discloses the polynucleotide sequence (SEQ ID NO:1) that encodes a dual specificity phosphatase-14 polypeptide (see SEQ ID NO:2) and discloses that the DSP-14 polypeptide is capable of dephosphorylating a DSP-14 substrate (*see, e.g.,* page 6, line 25 through page 7, line 3). As taught in the instant Application and presented in the Declaration submitted herewith, the claimed DSP-14 polynucleotide may be inserted into an expression vector that is transfected into a host cell to produce the DSP-14 polypeptide (*see, e.g.*, page 9, line 8 through page 10, line 2). The expressed polypeptide can then be analyzed for its ability to dephosphorylate a suitable substrate according to assays for detecting DSP-14 activity, which are also described in the specification (*see, e.g.,* page 18, line 1 through page 19, line 24) and in the Declaration. In addition, the specification enables the cloning and expression of DSP-14 substrate trapping mutants, which may be used for characterizing and identifying DSP-14 substrates and for identifying agents that alter intracellular molecular signaling by modulating DSP-14 activity. (*See, e.g.*, at page 7, line 12 through page 8, line 5; page 37, line 7 through

page 40, line 12). Applicants submit that all of the aforementioned methods may be performed by permissible routine screening and without undue experimentation.

Accordingly, Applicants respectfully submit that the claimed invention has a well-established and specific, substantial, and credible utility, which satisfies the requirements of 35 U.S.C. § 101. Applicants further submit that the specification enables a person having skill in the art to make and use the claimed invention in full compliance with 35 U.S.C. § 112, first paragraph. Therefore, Applicants respectfully request that the rejection of these claims be withdrawn.

Applicants respectfully submit that all claims remaining in the Application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. In the event that the Examiner believes a teleconference will facilitate prosecution of this case, the Examiner is invited to telephone the undersigned at (206) 622-4900.

Respectfully submitted,

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Enclosure:
Declaration under 37 C.F.R. § 1.132

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